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I. INTRODUCTION

In modern usage, the word "vaccine" is usually restricted to describe an immunogen administered to at-risk healthy subjects prior to their becoming exposed to a microbial pathogen. This word is also often used when the immunogen is administered early after exposure but before the onset of disease manifestations; in such circumstances the qualifying prefix "post-exposure" is employed.

Given the conventional use of the word "vaccine" the term "vaccine therapy" might seem to be an oxymoron. However, historical precedent suggests that the term "vaccine therapy" should be used to describe administration of a microbe-specific antigen for therapeutic purposes (after the onset of established disease) [1]. Indeed, the terms "vaccine therapy" or "vaccinotherapy" have been used continuously for this purpose as Medical Subject Headings in the Index Medicus since 1911. While alternative terms have been proposed (immunoregulation, immunotherapy, immunostimulation) these terms are overly general and fail to convey the meaning that the immunity sought in vaccine therapy is both active and directed against microbe-specific antigens.

Thus, vaccine usage can be categorized relative to the time of microbial exposure: (1) true prevention or prophylaxis, (2) post-exposure prophylaxis, and (3) therapy or reduction of recurrences. These different uses of vaccines are presented schematically in Figure 1.

While there is no question of the clinical efficacy of vaccination before exposure, and reasonable proof for clinical efficacy of vaccination for post-exposure prophylaxis, there is at present no uncontested evidence for clinical efficacy of vaccination for therapy or reduction of recurrences in any overt human disease. Nonetheless, the concept that the immune response might be accessible to medical intervention is an appealing one. The recent

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67

Vaccine Therapy

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> *The physician of the future will, I foresee, take upon himself the role of an immunizator.*
> —Sir Almroth Wright, 1902
>
> *History doesn't repeat itself, but it rhymes.*
> —Anon

I. INTRODUCTION

In modern usage, the word *vaccine* is usually restricted to describe an immunogen administered to healthy subjects at risk prior to their becoming exposed to a microbial pathogen. This word is also often used when the immunogen is administered early after exposure but before the onset of disease manifestations; in such circumstances the qualifying prefix *postexposure* is employed.

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While there is no question of the clinical efficacy of vaccination before exposure and reasonable proof for clinical efficacy of vaccination for postexposure prophylaxis, there is at present no uncontested evidence for clinical efficacy of vaccination for therapy or reduction of recurrences in any overt human disease. Nonetheless, the concept that the immune response might be accessible to medical intervention is an appealing one. The recent development of technologies for production of large quantities of molecularly cloned and expressed antigens has led to a renewed interest in vaccine therapy [2]. This chapter reviews the usage of vaccines after the moment of exposure (infection). The emphasis is on therapeutic use of vaccines, but postexposure vaccination is also reviewed for purpose of comparison.

II. HISTORY OF VACCINE THERAPY

Edward Jenner, in his epochal 1798–1800 papers on the use of vaccinia in preventing smallpox, briefly commented on the apparent success of postexposure vaccination (see below) to prevent clinical smallpox [3]. However, he never proposed treatment of established smallpox with vaccinia.

The now obscure French syphilologist Joseph-Alexandre Auzias-Turenne read Jenner and saw parallels between the benign and fatal pox disease vari-
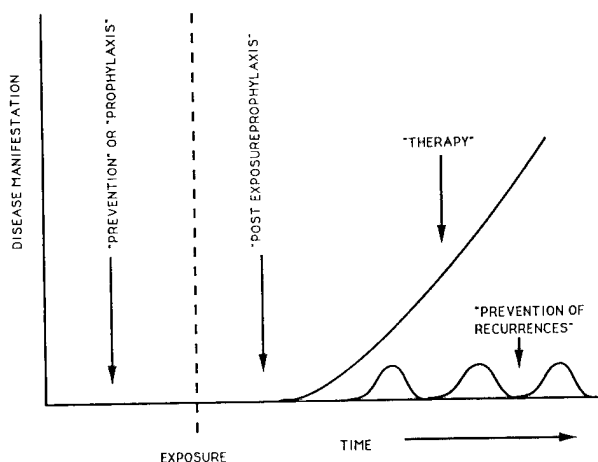
Figure 1 Diagram of the possible uses of vaccines relative to the time of exposure to an infectious agent.

ants and the benign and fatal variants of genital chancres. He proposed that matter from benign chancres could be used as prophylaxis against or even treatment of syphilis. He championed *syphilization*—an intentional contraction of the terms *syphilis* and *vaccination*—as a public health tool [4,5]. For therapy he proposed that matter from a benign lesion could be inoculated serially, up to dozens of times, into the skin of a patient with established syphilis in an effort to achieve a cure. "Syphilization" was a major topic of debate at the 1st International Medical Congress in Paris in 1867. Of course, the clinical efficacy of his approach was never proved or even fully accepted, because he clearly confused syphilis with chancroid and genital herpes.

At Louis Pasteur was beginning his studies of vaccines in the late 1870s, he chanced to receive a copy of Auzias-Turenne's collected works. Pasteur's nephew and laboratory assistant Adrian Loir contends that Pasteur read this book avidly and that he was greatly influenced by Auzias' ideas [6]. Loir reports that Pasteur repeated some of Auzias' experiments of pre- and postexposure immunization, particularly with bovine pleuropneumonia [7]. Pasteur also almost certainly read Auzias' speculative paper (written in 1864) on possible uses of material from rabies-infected tissues for purposes of therapeutic vaccination [4,8].

Pasteur's success in the postexposure prophylaxis in the case of 9-year-old Joseph Meister is now legendary; it immediately led to widespread acceptance of postexposure vaccination for rabies [9,10]. However, less widely known is the fact that Pasteur—perhaps inspired by Auzias—had already used a rabbit brain rabies vaccine in attempts to treat

two cases of clinically apparent rabies [11]. These two cases are probably the first true trials of antigen-specific "vaccine therapy." One patient died less than a day after receiving the therapy but the other apparently survived. Pasteur never published or otherwise publicly reported on these cases; they were found only recently by Geison in Pasteur's laboratory notebooks. Geison speculates that Pasteur kept these cases secret because he was not absolutely sure about the accuracy of the diagnosis in the one treated "rabies" patient who survived.

Not to be outdone by Pasteur, Robert Koch reported in 1890 that he had discovered a cure for tuberculosis, an announcement that rocked the medical world [12–16]. Initially he refused to reveal the exact chemical composition of his cure, referring to it only as a "brownish clear fluid." He provided samples of the fluid to prominent physicians around Europe for their experimental use (foreshadowing today's "parallel track" for investigational therapies). Tuberculosis patients from around the world flocked to Berlin to receive the treatment from Professor Koch. Only months later did he reveal that the cure was a solution or suspension of glycerin and extracts from tubercle bacillus cultures, a composition similar to what is now referred to as "tuberculin." Like Pasteur, Koch had reported that microbe-derived antigens could be used to stimulate immunity in patients who were already infected. However, reports from colleagues using the material were less than enthusiastic [17]. Cures and remissions were infrequent, and severe reactions including several deaths, were commonplace. While tuberculin was a failure as a vaccine therapy, these trials led to its use as a diagnostic reagent and opened the field of delayed-type hypersensitivity.

Impressed by Koch's experiments, Almroth Wright in England developed vaccine therapies for other microbes that could be cultivated in vitro [18,19]. In a 1902 paper subtitled "Generally on the treatment of localized bacterial invasions by the therapeutic inoculation of the corresponding bacterial vaccine," he reported the use of heat-killed cultures of *Staphylococcus aureus* as a vaccine therapy [20]. Using an assay developed by William Boog Leishman, he measured the ability of sera to facilitate the ingestion of bacteria by leukocytes. He coined the term *opsonization* for this activity and correlated changes in the serum opsonic index with outcome in his vaccine therapy patients [21]. Almroth Wright became a zealous champion of vaccine therapy; the title of his biography by Zachary Cope is *Almroth Wright, Founder of Modern Vaccine Therapy* [22].

Based on his discussions with Wright, George Bernard Shaw wrote *The Doctor's Dilemma*, a play whose

plot revolved around the selection of patients for slots in a tuberculosis vaccine therapy trial [23]. One memorable line from this play—a vaccine therapist's credo—reads: "There is at bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes. Stimulate the phagocytes. Drugs are a delusion." Of course, not everyone was persuaded by Sir Almroth Wright's data. One wag dubbed him "Sir Almost Wright."

Vaccine therapy flourished during the first decades of the twentieth century (Figure 2). Even Alexander Fleming, later to discover penicillin, wrote an effusive testimonial about its virtues [24]. A new *Journal of Vaccine Therapy* appeared, and textbooks with guidelines on vaccine therapy for general practitioners were published. Pharmaceutical companies advertised various concoctions of mixtures of heat-inactivated organisms, typically 10 to 100 million per inoculation, for use as therapeutic vaccines [25,26]. Different mixtures were to be used for different disease syndromes—for pneumonia, urinary tract infections, or skin infections—somewhat as today different antibiotic regimens are recommended for initial therapy of infections at these different sites. Surveys revealed that two-thirds of U.S. practitioners used vaccine therapy in their practice, most often for furunculosis or tuberculosis [27].

Despite their widespread use, bacterial therapeutic vaccines were never proved to have clinical efficacy. The bountiful early literature on vaccine therapy is difficult to interpret due to the total lack of appropriately controlled trials. Although vaccine immunogenicity in the setting of established disease is also difficult to assess from these earlier reports, the anecdotal data amassed are nontheless impressive. Clinicians who used tuberculin vaccine therapy frequently reported increased inflammation at the sites of clinical tuberculosis, especially at readily visible sites on the skin [28]. Similarly, Wright and coworkers show reproducible increases in the serum opsonic index in *Staphylococcus* trials [29,30]. Some experimental studies in animal models also suggested immunogenicity (but none showed proof of efficacy) [31].

Enthusiasm for vaccine therapy waned substantially when a variety of potent antibiotics such as streptomycin, chloramphenicol, and penicillin were discovered and developed. It can be fairly said that Almroth Wright's death in 1947 marked the end of the golden era of vaccine therapy. In the 1950s and 1960s there continued to be sporadic efforts to develop and test therapeutic vaccines for various viral and fungal infections—diseases for which there were no antibiotics—but none showed much promise [32–38]. Furthermore, careful controlled trials of recurrent furunculosis with staphylococcal vaccine therapy (by Sanford and others) failed to detect clinical efficacy [39]. By the 1970s, antibiotic treatment completely eclipsed antigen-specific treatment, and vaccine therapy became a forgotten art.

III. EFFICACY OF VACCINATION FOR POSTEXPOSURE PROPHYLAXIS

The observation that vaccination *after* exposure to an infectious agent can afford protection against clinical disease carries obvious implications for a general understanding about how vaccines work: complete or "sterilizing" immunity, with total suppression the very first rounds of microbe replication, is not necessary for a vaccine to be effective. This, in turn, suggests that in some circumstances vaccines might be useful even later in the course of an infection, for therapy of overt disease.

There is reasonable evidence for the efficacy of for postexposure vaccination in at least four human infectious diseases. All four are viral infections where an exact time of exposure can be determined with relative ease, the incubation period is at least 2 weeks, and an effective vaccine is available. Because these reports on postexposure vaccination are the only evidence that vaccines can be effective after rather than before infection, they are presented here in some detail, in historical order.

SECURITY

For a period of several thousand years, castles and walled towns were the only havens of security against armed violence.

Modern life has its own problems of security. The development of cheap and rapid transportation, together with the tremendous concentration of population in our industrial areas, has greatly increased the hazards of epidemic disease.

Vaccinotherapy can greatly diminish these dangers. Its possibilities are only beginning to be realized.
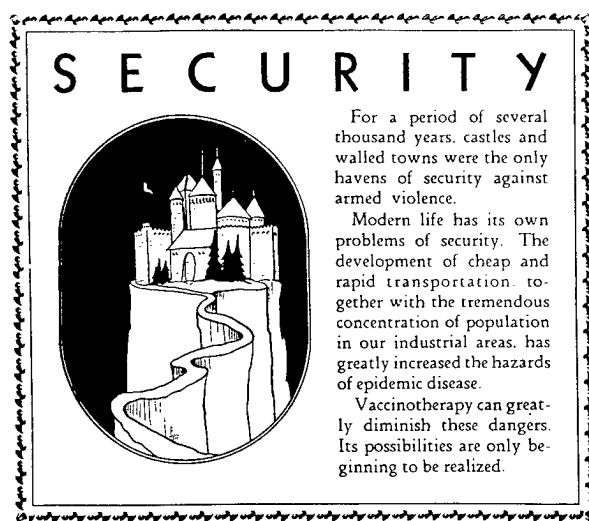
Figure 2 Magazine advertisement for "vaccinotherapy" products, 1931.

A. Smallpox

In Edward Jenner's third paper on vaccination against smallpox, in 1800, he presented the first anecdotal evidence for efficacy of postexposure vaccination [3]: "Some striking instances of the power of the cow-pox in suspending the progress of the smallpox after the patients had been several days casually exposed to the infection have been laid before me. . . ."

The first case recounted by Jenner was reported to him by Mr. Lyford, a Winchester surgeon. He vaccinated two small children who were in close contact with their father, who had been ill for 5 days. Lyford commented that he was "surprised to find the vaccine disease advance and go through its regular course . . . to the total extinction of the smallpox." Jenner also recounted a case reported to him by his nephews, the Reverend G. C. Jenner and Mr. H. Jenner, who vaccinated a father, mother, and five children 4 days after another child in the family had developed a smallpox eruption. Vaccination did not take in the mother, and she developed smallpox. Vaccination took in all four children and the father, and all remained healthy, despite their continuous contact with smallpox in the child and the mother.

The largest and most detailed study of postexposure vaccination against smallpox was conducted by Dr. William Hanna, Medical Office of the Port of Liverpool, who collected 75 cases [40]. Most were travelers from Boston who landed incubating smallpox during the severe outbreak in that city in 1902–1903. All were promptly vaccinated regardless of the time since exposure and then confined to the Port Isolation Hospital. Among those who were previously vaccinia-naive and vaccinated within 6 days of exposure, all 10 of 10 developed only mild or moderate disease; of those vaccinated within 7–14 days of exposure but before rash, 7 developed mild/moderate and 6 severe disease (1 death); of those vaccinated only after the rash had begun, 3 developed moderate and 4 severe disease (2 deaths).

Among those who had previously been vaccinated and then revaccinated within 6 days of exposure, 10 developed mild disease, 2 moderate, and one severe disease; of those revaccinated within 7–14 days of exposure but before rash, 14 developed mild disease and one moderate disease; and of those revaccinated only after the rash had begun, 7 developed mild disease and 10 moderate disease.

Evidence of a successful vaccine "take"—local vesiculation—during the incubation period also correlated strongly with protection against severe disease in the vaccinia-naive cases [40]. Among those not previously vaccinated, a successful take during the incubation period led to severe disease in only 2 of 19, whereas an unsuccessful vaccination (which occurred typically in those cases vaccinated later after exposure, often where symptoms had already begun) led to severe disease in 8 of 11.

Dixon reported on the efficacy of postexposure vaccination in Tripoli in 1946 and compared the spectrum of disease severity among persons who had never been vaccinated to that among those who were successfully vaccinated postexposure [41]. His findings were remarkably similar to those of Hanna: among 21 cases successfully vaccinated with 5 days of exposure, all developed only mild illness. But when successful vaccination was not performed until the sixth to tenth day after contact (n = 36 cases), the spectrum of disease severity was not different from that among unvaccinated persons.

For obvious ethical reasons, there are no prospective controlled trials of administration of vaccinia at different intervals after exposure, so precise data are impossible to obtain. The two retrospective series presented here identified cases for inclusion by the appearance of at least some smallpox papules. Persons with no evidence at all of smallpox would have been excluded. Indeed, the data in these two series may present a conservative estimate of the efficacy of postexposure vaccination against smallpox, because some individuals who that were completely protected would not have been counted.

Fenner pointed out that the clinical course of infection following intradermal vaccinia inoculation (fever in 6–7 days) is much more rapid than the clinical course of typical variola major in an unvaccinated subject (fever in 14 days) or even that of intradermal inoculation smallpox in a naive subject (10–12 days) [42]. He speculates that this alacrity of vaccinia might be an important factor in the success of postexposure vaccination against smallpox.

B. Rabies

Surprisingly, active vaccination for postexposure prophylaxis of rabies, widely considered to be the classic example of postexposure prophylaxis, is of uncertain clinical benefit. The history is convoluted, even for the expert. I shall do my best to summarize it here.

The first attempts at rabies postexposure prophylaxis in humans were conducted by Pasteur in mid-1885. As noted above, he had by this time already tried vaccine therapy of clinically apparent rabies in two patients, with inconclusive results [43]. He first used postexposure rabies vaccine on July 6 on Joseph Meister, who had been bitten 2 days earlier. The boy apparently did well. On October 20, Pasteur began

vaccination of his second case, this time the courageous teenager Jean-Baptiste Jupille, who had been severely bitten while defending a group of younger children from an apparently rabid dog. Six days later Pasteur announced his new method to a standing ovation at the Academy of Science in Paris. One eminent colleague took the floor to proclaim that date of October 26, 1885, would live "forever memorable in the history of medicine and forever glorious for French science." Pasteur had presented only two clinical cases, with follow-up periods of 4 months and 1 week, respectively. During the next year, over 2000 rabies-exposed patients from all over Europe flocked to Paris to receive the postexposure vaccination. No controlled clinical studies were done.

Geison, through careful study of Pasteur's laboratory notebooks, has recently shown that there are serious reasons to doubt the efficacy of Pasteur's original postexposure vaccine [44]. The first were "scientific" concerns. For treatment of Meister and Jupille, Pasteur employed a 14-day series of injections of ground up rabid spinal cords taken from rabbits intracranially inoculated with a "fixed" (rabbit brain–adapted) rabies virus. For the human cases, he began with 14-day dried rabbit cord and progressively each day inoculated a 1-day fresher cord until, on the last day, he inoculated fresh rabbit brains. Although never clearly expounded, his theory was that he was inoculating successively "less attenuated" virus each day. Modern authorities have established that rabbit brain–fixed virus can be virulent for humans. Most of Pasteur's colleagues assumed that his animal experimental work had laid a careful foundation for postexposure rabies vaccination of bitten humans. However, at the time he treated Joseph Meister, Pasteur had not tested the efficacy of the regimen used on him in animals but instead only a variety of other exploratory vaccines and regimens.

Furthermore, there are also questions about the statistical significance of Pasteur's animal experiments [44]. Geison has calculated the success rate of these earlier vaccines for postexposure protection of dogs against challenge (which was the bite of a rabid dog). Among vaccinated dogs, 16 of 26 (62%) remained rabies-free. However, among untreated control dogs, 4 of 7 (57%) also remained rabies-free. Thus, although Pasteur had no real scientific evidence for the efficacy of postexposure rabies vaccination at the time he treated Meister, the method promptly became the standard of care.

Serious concerns (and lawsuits stemming from those concerns) were promptly raised about rabies cases in humans that occurred in spite or perhaps because of the Pasteur vaccine. Within a few years,

the Pasteur Institute switched to a carbolic acid–inactivated vaccine. Nonetheless, the bulk of uncontrolled clinical data on postexposure rabies vaccination suggested that the method was reasonably safe and (arguably) effective.

Webster, of the Rockefeller Institute for Medical Research in New York, in 1939 carefully reviewed the world's literature on experimental rabies postexposure vaccination in animal models [45,46]. He concluded that "it appears that Pasteur's tests on the immunization of dogs by vaccination following bite have not been confirmed. Nine workers over a period of 50 years have stressed the relatively unsatisfactory results obtained in a series of over ninety experiments."

McKendrick in 1940 reviewed results of the first 1 million rabies postexposure vaccinations at Pasteur institutes throughout the world [47]. He reported in the *Bulletin of the Health Organization of the League of Nations* that there were no differences in rabies mortality with respect to the type of vaccine employed (killed, live, heated, or other), regardless of the probability of the presence of rabies in the biting animal, location, or severity of the bite. Furthermore, delay in commencing vaccine treatment, even beyond 14 days, failed to show increases in rabies mortality. Webster commented that "These findings lead to the inference that these vaccines are all either equally effective or equally noneffective—both disturbing conclusions." Other smaller but more detailed studies also failed to demonstrate any significant efficacy of postexposure rabies vaccination in humans [48].

Although passive postexposure immunization with antirabies immune serum was used sporadically as early as the 1890s, it was not until the 1950s that the efficacy of antirabies serum was studied in controlled field trials in humans [49,50]. Wolf-bite victims were solidly protected by postexposure vaccine plus serum but not by vaccine alone. Subsequent experimental studies of rabies in dogs and in mice have shown that passive immunity with serum and active immunity with vaccine are synergistic when given in the right doses [51,52].

There have been no controlled trials, or even uncontrolled trials, of the newer, safer "third-generation" cell culture–grown rabies vaccines alone (without passive antibodies) for postexposure vaccination. Current recommendations for rabies postexposure prophylaxis call for simultaneous administration of rabies immune globulin, regardless of the type (human diploid cell, Vero cell, rhesus diploid cell), route (intramuscular or intradermal), or dose of vaccine. Early experience with vaccinia and canarypox-vectored rabies proteins suggests that these genetically engineered vaccines might

have an advantage in prompt stimulation of antirabies immunity [53,54].

C. Hepatitis B Virus

By comparison to rabies, the history of hepatitis B virus (HBV) postexposure vaccination is relatively straightforward; evidence for postexposure efficacy was found in the first prevention vaccine trials. In 1978–1980, a randomized, placebo-controlled, double-blind study of plasma-derived vaccine was conducted among 1083 homosexual men in New York who were known to be at risk for HBV infection [55]. The overall reduction in incident infections was as high as 92%. Hepatitis B events occurring in the first 75 days after the first vaccine injection were analyzed as a subset, since these were thought to be HBV infections that were incubating at the time of vaccination. Although the total incidence of new infections in the first 75 days was not reduced by vaccination, disease severity was substantially less in vaccine recipients than placebo recipients. The numbers of volunteers with HBV events with different disease severities were as follows:

● Seroconversion to HBc only, without HBs antigenemia and without ALT elevation (6 vaccine versus 0 placebo)

● HBs antigenemia, with no or minimal ALT elevation (3 vaccine versus 3 placebo)

● HBs antigenemia with hepatitis (2 vaccine versus 10 placebo)

In this study, analysis of events within the first 45 days also showed a trend toward milder disease among vaccine recipients, but the number of events was to small for tests of significance.

The same postexposure protective effect was found among early infections in another study of the plasma-derived vaccine conducted among 1402 homosexual men in five American cities in 1980–1981 [56]. Among placebo recipients there were 28 HBV events, all of which were HBs antigenemic and 25 of which were accompanied by ALT elevations. In contrast, of the 27 events in vaccine recipients during the same time period, only 17 were HBs antigen–positive.

After the plasma-derived vaccine was proved efficacious, it became difficult to prove the efficacy of the newer genetically engineered HBV vaccines in placebo-controlled trials. Recent data from a placebo-controlled trial and a comparative trial (compared to plasma-derived vaccine) in China have shwn that yeast-expressed recombinant HBV vaccine was highly efficacious in postexposure prophylaxis to prevent chronic perinatal HBV infection [57,58].

Although vaccine alone is efficacious in postexposure prophylaxis of HBV, current recommendations call for the addition of hepatitis B immune globulin to vaccine for postexposure prophylaxis of HBV to provide greater effect.

D. Varicella

Evidence for the efficacy of postexposure vaccination against varicella has also been directly demonstrated in several studies. In one early study where vaccine was administered within 3 days of exposure, protective efficacy against disease was very high, essentially 100% [59]. Subsequent studies have shown that protective efficacy against disease is directly related to how soon after exposure the vaccine is administered and how much vaccine virus is administered [60]. When a dose of vaccine greater than 1000 plaque-forming units is administered within 3 days of exposure, postexposure protection is excellent.

Although postexposure vaccination against varicella is an efficacious strategy, preexposure vaccination is recommended for persons at risk as a more reliable approach.

E. Vaccine Therapy for Infections That Are Preventable or Modifiable by Postexposure Vaccination

There is no evidence that the vaccination of patients with clinically overt smallpox, rabies, or varicella has any favorable impact on disease course. Similarly, most studies of chronic HBV infection have not recorded any beneficial effect of immunization. However, there is one unconfirmed report of sustained clearing of HBs antigen and normalization of liver function tests attributed to vaccine therapy in eight patients [61].

IV. CONTEMPORARY VACCINE THERAPY EFFORTS

Although vaccine therapy receded into the scientific backwaters in the 1960s and 1970s, some lines of research never fully disappeared. Also, new findings in immunology and molecular biology have prompted a modest resurgence of interest in vaccine therapy for the treatment of chronic infectious diseases. Today there are significant ongoing efforts to develop and test therapeutic vaccines for several problems of public health significance. Because there is no solid proof of

efficacy for any of the therapeutic vaccines in these studies, they are reviewed here in outline form only.

A. Leprosy

In studies of the immunology of tuberculoid and lepromatous leprosy, Convit in Venezuela observed that patients with lepromatous leprosy did not clear heat-inactivated *Mycobacterium leprae* organisms that were experimentally inoculated intradermally [62,63]. However, these patients did clear inoculated five attenuated bacille Calmette-Guérin (BCG). When heat-killed *M. leprae* were mixed with the live BCG, the *M. leprae* were also cleared. Other studies suggested that *M. leprae* was directly suppressive of a delayed-type hypersensitivity response [64–70]. These experimental observations led to clinical trials of vaccine therapy of leprosy in which mixtures of *M. leprae* and BCG were inoculated into hundreds of patients [71,72]. Although treated patients showed improvements in a number of measures of antileprosy immunity—such as increased antibody titers, increased skin-test reactivity, and increased specific lymphocyte proliferation—clinical benefits were not clear-cut. Combined chemotherapy and vaccine therapy is reported to lead to shorter duration of treatment and faster hospital release [73–75].

Injections of 5 units of purified oxygen derivative of tuberculin also lead to clearing of *M. leprae* at the site of inoculation, as do injections of other mycobacterial antigen preparations [76–78]. Fine and Smith have expressed the opinion that widespread use of BCG has been a significant factor in the decline in incidence of leprosy in many countries [79].

B. Tuberculosis

Vaccine therapy for tuberculosis, championed by Koch and widely employed for decades, is undergoing yet another revival, intradermal injections of *Mycobacterium vaccae* have been used to boost immunity to *Mycobacterium tuberculosis* in symptomatic patients [80–82]. The method has been aggressively pursued as cost-effective for developing countries [83,84]. Also, vaccine therapy is seen as perhaps the only alternative for patients infected with multidrug–resistant bacilli [85]. Combination of second-line antituberculosis drugs with vaccine therapy has been reported to give satisfactory results.

C. Leishmaniasis

Convit noted the similarities between the clinical and histopathological features of leprosy and cutaneous leishmaniasis and hypothesized that the pathogenesis of the two diseases was similar. Given the apparent success of treatment of leprosy with BCG, Convit and colleagues conducted clinical trials of vaccine therapy for leishmaniasis with inoculations of BCG mixed with killed *Leishmania* promastigotes [86–89]. Although in vitro markers of antileishmanial immunity have not shown marked changes, clinical efficacy in one study was reported to be excellent [90,91]. Other studies with soluble leishmanial antigens have found evidence of clinical efficacy [92].

D. Papillomaviruses

Vaccine therapy for cutaneous warts in cattle has been a common veterinary practice for decades [93]. Infections with bovine papillomavirus typically results in benign lesions that regress spontaneously. Occasionally warts can persist and give rise to squamous cell carcinomas. Commercial therapeutic wart vaccines were widely used but had questionable efficacy. Autogenous vaccines, made from glycerol-saline suspensions of lesions, were reported to have excellent efficacy and were recommended by experts [94,95]. More recent efforts have focused on the development and testing of recombinant bovine papillomavirus proteins and viruslike particles, but none has thus far been proved to have clinical efficacy [96–98].

In the laboratory, the cottontail rabbit papillomavirus is a major model for cancer associated with papillomaviruses. Recent studies have shown that therapeutic vaccination with homologous nonstructural proteins can induce regression in virus-induced papillomas [99].

Apparent successes of therapeutic papillomavirus vaccines in animals has provoked a continued interest in development of therapeutic papillomavirus vaccines [100–103]. Autogenous vaccines continue to be used as experimental therapy in humans. One recent report proposed that excision followed by autogenous tissue vaccine is the most effective treatment for perianal condyloma acuminata [104]. Special efforts are being made to develop a vaccine for prevention and therapy of human papillomavirus type 16, since this type is strongly associated with cervical carcinoma. At least two Phase I clinical trials have been initiated with vaccinia/HPV-16 early antigen recombinant vaccines [105].

E. Herpes Simplex

Because recurrent herpes infections are thought to occur as a consequence of a decline in antiherpes im-

munity, this disease has been an attractive target for vaccine therapy. Numerous therapeutic herpes vaccines produced by inactivation of cell culture–grown virus have been tested humans [106]. Most early trials were inadequately controlled, and in those few clinical therapeutic herpes vaccine trials done where controls were adequate, results were inconsistent [107–110]. Nonetheless, there continue to be reports in the medical literature of uncontrolled series of thousands of patients treated with therapeutic herpes simplex vaccines [111].

Recent efforts have focused on the development and testing of herpes subunit protein vaccines. Vaccines constructed from recombinant-expressed surface glycoproteins, when properly adjuvanted, have reduced the number of recurrences in the guinea pig genital infection model and in the rabbit ocular infection model [112–122]. Initial trials in humans demonstrated that these vaccines stimulated immune responses similar to those seen in natural infections. A placebo-controlled trial of a recombinant glycoprotein D of herpes type 2 with alum adjuvant was done with follow-up for 1 year [123]. Vaccinees reported 25% fewer recurrences than placebo recipients.

F. Human Immunodeficiency Virus

When acquired immunodeficiency syndrome (AIDS) was discovered to be caused by human immunodeficiency virus type 1 (HIV-1) and it became understood that symptomatic illness was the end stage of a slow but inexorable progressive viral infection, several groups began vaccine therapy trials. The vaccines tested thus far have spanned the full gamut of historical approaches previously taken for other therapeutic vaccines, including crude unpurified preparations, inactivated virions, protein subunits, and genetically engineered replicating vectors.

Attempts have been made to treat HIV with crude infusions of infected whole blood or materials derived from blood [124–126]. One approach has been to autovaccinate patients with autologous-inactivated HIV obtained by cytapheresis of the patient's blood, in an effort to stimulate immunity against the patient's own viral quasispecies. Another approach has been to infuse infected blood taken directly from patients with stable asymptomatic infections into patients with advanced disease, in the hope that the newly introduced virus would be more immunogenic and provoke an effective immune response. There is little evidence that these attempts at therapeutic vaccinations with blood products had any favorable impact.

More promising initial results were obtained by vaccine therapy with inactivated antigens or subunit

proteins. Zagury and colleagues immunized patients with paraformaldehyde-fixed autologous lymphocytes that expressed genetically cloned vaccinia-expressed HIV antigens [127–130]. Salk and colleagues inoculated patients with purified inactivated cell-culture whole virions [131–135. Redfield and Birx in my own group injected patients with a genetically engineered HIV surface envelope protein that had been expressed in insect cells [136–138]. Other safety and immunogenicity HIV vaccine therapy trials have been done with HIV envelope proteins expressed in Chinese hamster ovary cells, envelope proteins expressed from Vero cells infected with recombinant vaccinia, and core protein expressed in yeast [139–147]. In total, at least 10 Phase I trials have been completed and 7 Phase II trials have been undertaken, but not all have been reported in the literature.

All of the protein subunit and inactivated whole HIV virion candidate therapeutic vaccines have been safe. However, incomplete inactivation of the vaccinia vector in one trial led to serious complications in severely immune-compromised patients [148]. All of the candidate inactivated virion or protein subunit vaccines evaluated showed increases in specific antibody titers, most easily detected as rises to specific epitopes, and increased in vitro lymphocyte proliferative responses to vaccine antigen. Boosts in measures of functional immunity such as neutralizing antibody and cytotoxic lymphocyte activity have been detected, but only infrequently.

Unfortunately, the promise of HIV therapeutic vaccination with HIV-specific antigens hinted at by the results of these Phase I trials has not been borne out in placebo-controlled Phase II trials. Five trials have now been completed, and none has found clear evidence of clinical efficacy as measured by rises in blood CD4 lymphocyte counts, lowering of plasma HIV genomic RNA levels, or decreased incidence of opportunistic infections.

Although lacking in clinical efficacy, HIV vaccine therapy with protein subunit vaccines can also be used as a probe to dissect the immune response to HIV. New antibodies stimulated by vaccine therapy with recombinant subunit envelope proteins have been found to be directed against linear epitopes, compared to natural antibodies which predominantly bind to conformational epitopes [149–153]. These results suggest that the current generation of genetically engineered subunits proteins may have to be redesigned so as to present more native conformations or that new adjuvants may have to be developed that more faithfully preserve conformational determinants.

"Gene therapy" has also been tried to boost anti-HIV immunity in infected patients [154,155]. In this

approach genes encoding for specific HIV antigens are expressed in vivo in patients cells. Initial cautious trials have been done by transduction of HIV genes into patient fibroblasts ex vivo and then transplanting the cells into the patient. There is no clear results from these preliminary trials.

Last, mathematical modeling studies have suggested that it may be possible to introduce rapidly replicating but nonpathogenic HIV variants in vivo into already infected patients, to compete with and thereby reduce the replication of the endogenous pathogenic variants [156]. The exceptional ability of HIV to recombine genetically would suggest that this approach, or any similar therapeutic approach employing replicating agents, should be entertained only with great caution.

V. SUMMARY AND CONCLUSIONS

Since the blossoming of microbiology as a laboratory science, vaccine therapy has been an alluring concept. The seminal thinkers of the field including Pasteur, Koch, and Wright were all drawn to the idea that it should be possible to manipulate and direct the immune response in ways favorable to the patient. Disappointingly, their dreams have yet to be realized.

Will vaccine therapy ever live up to its conceptual promise? One skeptical line of reasoning posits that the human immune response—the results of millions of years of natural selection by microbial pathogens—will be difficult or impossible to improve upon. However, this reasoning fails to consider that the microbes have continually evolved as well. The same forces of natural selection that produced the human immune system are also continuously at work to produce microbes with refined ability to exploit weaknesses in that system through suppression, diversion, or evasion. Like the Red Queen in *Through the Looking Glass*—who runs but doesn't get far because the landscape moves with her—the human immune response has evolved, but the microbial landscape has evolved apace.

If effective therapeutic vaccines are to be developed, it seems that this will require a more complete understanding of the mechanisms that microbes use to establish and maintain chronic steady-state infections. Thoughtful new vaccine designs may be necessary to counter suppression, reinforce subverted costimulatory signals, or escort antigens in correct conformations to responsive cells. Indeed, vaccine therapy may not only be a goal in itself but, following the precedent set by Pasteur, Koch, and Wright, may also be a valuable tool

to dissect the host-pathogen relationship so as to understand its crucial facets.

REFERENCES

1. Burke DS. Vaccine therapy for HIV: A historical review of the treatment of infectious diseases by active specific immunization with microbe-derived antigens. Vaccine 1993; 11:883–891.
2. Cohen J. Vaccines get a new twist. Science 1994; 264:503–505.
3. Jenner E. A continuation of facts and observations relative to the variole vaccinae, or cow-pox, 1800. In: Eliot CW, ed. The Harvard Classics, Scientific Papers. Vol 38. New York: Collier, 1910.
4. Burke DS. Joseph-Alexander Auzias-Turrenne, Louis Pasteur, and early concepts of virulence, attenuation, and vaccines. Perspect Biol Med 1996; 39:171–186.
5. Auzias-Turenne JA. La Syphilisation. Publication d l'Oeuvre du Docteur Auzias-Turenne: Faite par les Soins de ses Amis. (Syphilization, The collected works of Dr. Auzias-Turenne: Compiled through the efforts of his friends). Paris: Librairie Germer Bailliere, 1878:3–5.
6. Loir a. A l'ombre de Pasteur, la documentation medicale de Pasteur. (In the shadow of Pasteur: Pasteur's Medical Sources.) Mouve Sanit 1937; 14:387–392.
7. Loir A. Recherches sur le charbon et sur la peripneumonie bovine. Arch Med Exp 1892; 4:813–826.
8. Auzias-Turenne JA, La Syphilisation. Publication d l'Oeuvre du Docteur Auzias-Terenne: Faite par les Soins de ses Amis. (Syphilization, The collected works of Dr. Auzias-Turenne: Compiled through the efforts of his friends). Paris: Librairie Germer Bailliere, 1878:751–753.
9. Vallery-Radot R. La Vie de Pasteur. Paris: Librairie Hachette. 1924:619–621.
10. Dubos RJ. Louis Pasteur, Free Lance of Science. Boston: Little, Brown, 1951:326.
11. Geison G. The Private Science of Louis Pasteur. Princeton, NJ: Princeton University Press, 1995: 177–205.
12. Burke DS. Of postulates and peccadilloes: Robert Koch and vaccine (tuberculin) therapy for tuberculosis. Vaccine 1993; 11:795–804.
13. Koch R. Uber bakteriologische Forschung. (On bacterial research.) English translation of address delivered to the Tenth International Medical Congress, Berlin, August 1890. In: Carter KC, ed. Essays of Robert Koch. Westport, CT: Greenwood Press, 1987:179–186.
14. Minard EJC. The tenth international congress at Berlin, as I saw it. JAMA 1891; 16:589–591.
15. Koch R. Fortsetzung der Mittheilungen uber das Tuberkulin. (Continuation of the announcement

concerning a cure for tuberculosis.) Dtsch Med Wochenschr 1891; 15 January:101–102.

16. Koch R. Weitere Mitteilung uber das Tuberkulin. (Additional information about tuberculin.) Dtsch Med Wochenschr 1891; 22 October:1189–1192.

17. Anonymous. Official report on the results of Koch's treatment in Prussia. JAMA 1891; 11 Apr: 526–529.

18. Wright AE. Vaccine therapy: Its administration, value, and limitations. Proc R Soc Med 1910; 3: 1–38.

19. Colebrook L. Almroth Wright: Provocative Doctor and Thinker. London: Heinemann, 1954:47–61.

20. Wright AE. Notes on the treatment of furunculosis, sycosis, and acne by the inoculation of a staphylococcus vaccine, and generally on the treatment of localized bacterial invasions by therapeutic inoculations of the corresponding bacterial vaccines. Lancet 1902; 1:874–884.

21. Keating P. Vaccine therapy and the problem of opsonins. J Hist Med Allied Sci 1988; 43:275–296.

22. Cope Z. Almroth Wright: Founder of Modern Vaccine-Therapy. London: Thomas Nelson, 1966: 43–45.

23. Shaw B. 'The Doctor's Dilemma' (1906) with a Preface on Doctors. In Shaw B. Complete Plays with Prefaces. Vol 1. New York: Dodd, Mead, 1962.

24. Fleming A. Vaccine therapy in regard to general practice. Br Med J 1921; 19 February:255–259.

25. Sherman GH. The Bacterial Therapist: A Journal of Vaccine Therapy. Vol I. Detroit: Sherman, 1912.

26. Sherman GH. Vaccine News. Vols 1 and 2. Detroit: Sherman, 1931.

27. Hektoen L, Irons EE. Vaccine therapy: Result of a questionnaire to American physicians. JAMA 1929; 92:864–869.

28. Lister J. Lecture on Koch's treatment of tuberculosis. Lancet 1890; 68:1257–1259.

29. Wright AE. Vaccine therapy: Its administration, value, and limitations. Proc R Soc Med 1910; 3: 1–38.

30. Colebrook L. Almroth Wright: Provocative Doctor and Thinker. London: Heinemann, 1954.

31. Trudeau EL. The treatment of experimental tuberculosis by Koch's Tuberculin, Hunter's modifications, and other products of the tubercle bacillus. Trans Assoc Am Phys 1892; 87–101.

32. Lazar MP. Vaccination for recurrent herpes simplex infection. Arch Dermatol 1956; 73:70–71.

33. Goldman L. Reactions of autoinoculation for recurrent herpes simplex. Arch Dermatol 1961; 84: 1025–1026.

34. Kern AB and Schiff BL. Vaccine therapy in recurrent herpes simplex. Arch Dermatol 1964; 89: 844–845.

35. Miller RI. Treatment of equine phycomycosis by immunotherapy and surgery. Aust Vet J 1981; 57: 377–382.

36. Beemer AM, Davidson W, Kuttin ES, et al. Vaccine and mycostatin in treatment of cryptococcosis of the respiratory tract. Sabouraudia 1976; 14: 171–179.

37. Jesiotr M, Beemer AM. Vaccine and antimicrobial therapy in pulmonary nocardiosis. Scand J Respir Dis 1969; 50:54–60.

38. Beemer AM, Kuttin ES, Pinto M. Treatment with antifungal vaccines. Contrib Microb Immunol 1977; 4:136–146.

39. Bryant RE, Sanford JP, Alcoze T. Treatment of recurrent furunculosis with staphylococcal bacteriophage-lysed vaccine. JAMA 1965; 164: 123–126.

40. Hanna W. Studies of smallpox and vaccination. New York: William Wood, 1913.

41. Dixon CW. Smallpox in Tripolitania: An epidemiological and clinical study of 500 cases, including trials of penicillin treatment. J Hyg 1948; 46: 351–377.

42. Fenner F, Henderson DA, Arita I, et al. Smallpox and Its Eradication. Geneva: World Health Organization, 1988:65.

43. Geison G. The Private Science of Louis Pasteur. Princeton, NJ: Princeton University Press, 1995: 177–205.

44. Geison G. The Private Science of Louis Pasteur. Princeton, NJ: Princeton University Press, 1995: 234–253.

45. Webster LT. The immunizing potency of antirabies vaccines: A critical review. Am J Hyg 1939; 30(Sec B):113–134.

46. Webster LT. Rabies. New York: Macmillan, 1942.

47. McKendrick AG. A ninth analytical review of reports from Pasteur Institutes on the results of antirabies treatment. Bull Health Org League Nations 1940; 9:31–78.

48. Baltazard M, Ghodssi M. Prevention de la rage humaine. Rev Immunol 1953; 17:366–375.

49. Habel K, Koprowski H. Laboratory data supporting the clinical trial of antirabies serum in persons bitten by a rabid wolf. Bull WHO 1955; 13: 773–779.

50. Baltazard M, Bahmanyar M. Essai pratique du serum antirabique chez les mordus par loups enrages. Bull WHO 1955; 13:747–772.

51. Cho HC, Lawson KF. Protection of dogs against death from experimental rabies by postexposure administration of rabies vaccine and hyperimmune globulin (human). Can J Vet Res 1989; 52: 434–437.

52. Baer GM, Cleary WF. A model in mice for the pathogenesis and treatment of rabies. J Infect Dis 1972; 125:520–527.

53. Taylor J, Meignier B, Tartaglia J, et al. Biological and immunogenic properties of a canarypox-rabies recombinant, ALVAC-RG (vCP 65) in non-avian species. Vaccine 1995; 13:539–549.

54. Fujii H, Takita-Sonoda Y, Mifune K, et al. Protective efficacy in mice of post-exposure vaccination with vaccinia virus recombinant expressing either rabies virus glycoprotein or nucleoprotein. J Gen Virol 1994; 75:1339–1344.

55. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: Demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med 1980; 303: 833–841.

56. Francis DP, Hadler SC, Thompson SE, et al. The prevention of hepatitis B with vaccine: Report of the Centers for Disease Control Multi-center efficacy trial among homosexual men. Ann Intern Med 1982; 97:362–366.

57. Xu ZY, Duan SC, Margolis HS, et al. Long-term efficacy of active postexposure immunization of infants for prevention of hepatitis B virus infection. J Infect Dis 1995; 171:54–60.

58. Zhu QR, Gu XH, Duan SC, Xu HF. Long term immunogenicity and efficacy of recombinant yeast derived hepatitis B vaccine for interruption of mother-infant transmission of hepatitis B virus. Chin Med J 1994; 107:915–918.

59. Asano Y, Nakayama H, Yazaki T, et al. Protection against varicella in family contacts by immediate inoculation with live varicella vaccine. Pediatrics 1977; 59:1–8.

60. Asano Y, Hirose S, Iwayama S, et al. Protective effect of immediate inoculation of a live varicella vaccine in household contacts in relation to the viral dose and interval between exposure and vaccination. Biken J 1982; 25:43–45.

61. Pol S, Driss F, Michel M-L, et al. Specific vaccine therapy in chronic hepatitis B infection. Lancet 1994; 344:342.

62. Convit J, Aranzazu N, Pinardi M, Ulrich M. Immunological changes observed in indeterminate and lepromatous leprosy patients and Mitsuda-negative contacts after the inoculation of a mixture of Mycobacterium leprae and BCG. Clin Exp Immunol 1979; 36:214–220.

63. Rada EM, Convit J, Ulrich M, et al. Immunosuppression and cellular immunity reactions in leprosy patients treated with a mixture of Mycobacterium leprae and BCG. Int J Leprosy 1987; 55: 646–650.

64. Kaplan G, Sampaio EP, Walsh GP, et al. Influence of Mycobacterium leprae and its soluble products on the cutaneous responsiveness of leprosy patients to antigen and recombinant interleukin 2. Proc Natl Acad Sci USA 1989; 86:6269–6273.

65. Modlin RL, Kato H, Mehra V, et al. Genetically restricted suppressor T-cell clones derived from lepromatous leprosy lesions. Nature 1986; 322: 459–461.

66. Kaplan G, Grandhi RR, Weinstein DE, et al. Mycobacterium leprae antigen-induced suppression of T cell proliferation in vivo. J Immunol 1987; 138: 3028–3034.

67. Gelber RH, Mehra V, Bloom B, et al. Vaccination with pure Mycobacterium leprae proteins inhibits M. leprae multiplication in mouse footpads. Infect Immun 1994; 62:4250–4255.

68. Modlin RL. Th1-Th2 paradigm: Insights from leprosy. J Invest Dermatol 1994; 102:828–832.

69. Sieling PA, Abrams JS, Yamamura M, et al. Immunosuppressive roles for IL-10 and IL-4 in human infection: In vitro modulation of T cell responses in leprosy. J Immunol 1993; 150: 5501–5510.

70. Kaplan G. Cytokine regulation of disease progression in leprosy and tuberculosis. Immunobiology 1994; 191:564–568.

71. Convit J, Aranzazu N, Ulrich M, et al. Immunotherapy with a mixture of Mycobacterium leprae and BCG in different forms of leprosy and in Mitsuda-negative contacts. Int J Leprosy 1982; 50: 415–424.

72. Convit J, Aranzazu N, Zuniga M, et al. Immunotherapy and immunoprophylaxis of leprosy. Lepr Rev 1983; special issue:47S–60S.

73. Rada E, Ulrich M, Aranzazu N, et al. A longitudinal study of immunologic reactivity in leprosy patients treated with immunotherapy. Int J Lepr Mycobact Dis 1994; 64:552–558.

74. Kar HK, Sharma AK, Misra RS, et al. Reversal reaction in multibacillary leprosy patients following MDT with and without immunotherapy with a candidate for an antileprosy vaccine, Mycobacterium w. Lepr Rev 1993; 64:219–226.

75. Walia R, Sarathchandra KG, Pandey RM, et al. Field trials on the use of Mycobacterium w vaccine in conjunction with multidrug therapy in leprosy patients for immunotherapeutic and immunoprophylactic purposes. Lepr Rev 1993; 64: 302–311.

76. Kaplan G, Sheftel G, Job CK, et al. Efficacy of a cell-mediated reaction to the purified protein derivative of tuberculin in the disposal of Mycobacterium leprae from human skin. Proc Natl Acad Sci USA 1988; 85:5210–5214.

77. Zaheer SA, Misra RS, Sharma AK, et al. Immunotherapy with Mycobacterium w vaccine decreases the incidence and severity of type 2 (ENL) reactions. Lepr Rev 1993; 64:7–14.

78. Zaheer SA, Beena KR, Kar HK, et al. Addition of immunotherapy with Mycobacterium w vaccine to multi-drug therapy benefits multibacillary leprosy patients. Vaccine 1995; 13:1102–1110.

79. Fine PEM, Smith PG. Effiacy of leprosy vaccine. Lancet 1992; 360:406.

80. Stanford JL, Bahr GM, Rook GAW, et al. Immunotherapy with Mycobacterium vaccae as an adjunct to chemotherapy in the treatment of pulmonary tuberculosis. Tubercle 1990; 71:87–93.

81. Bahr GM, Shaaban MA, Gabriel M, et al. Improved immunotherapy for pulmonary tuberculosis with Mycobacterium vaccae. Tubercle 1990; 71:259–266.

82. Stanford JL, Stanford CA. Immunotherapy of tuberculosis with Mycobacterium vaccae NCTC 11659. Immunobiology 1994; 191:555–563.

83. Standford JL, Grange JM, and Pozniak A. Is Africa Lost? Lancet 1991; 338:557–558.

84. Onyebujoh PC, Abdulmumini T, Robinson S, et al. Immunotherapy with Mycobacterium vaccae as an addition to chemotherapy for the treatment of pulmonary tuberculosis under difficult conditions in Africa. Respir Med 1995; 89:199–207.

85. Prior JG, Khan AA, Cartwright KA, et al. Immunotherapy with Mycobacterium vaccae combined with second line chemotherapy in drug-resistant abdominal tuberculosis. J Infect 1995; 31:59–61.

86. Convit J. The Kellersberger Memorial Lecture. Leprosy and leishmaniasis: Similar clinical-immunological pathology. Ethiop Med J 1974; 12:187–195.

87. Convit J, Rondon A, Ulrich M, et al. Immunotherapy versus chemotherapy in localized cutaneous leishmaniasis. Lancet 1987; 1:401–405.

88. Convit J, Ulrich M. Antigen-specific immunodeficiency and its relation to the spectrum of American cutaneous leishmaniasis. Biol Res 1993; 26:159–166.

89. Modlin RL, Melancon-Kaplan J, Young SM, et al. Learning from lesions: Patterns of tissue inflammation in leprosy. Proc Natl Acad Sci USA 1988; 85:1213–1217.

90. Convit J, Castellanos PL, Ulrich M, et al. Immunotherapy of localized, intermediate, and diffuse forms of American cutaneous leishmaniasis. J Infect Dis 1989; 160:104–115.

91. Castes M, Moros Z, Martinez A, et al. Cell-mediated immunity in localized cutaneous leishmaniasis patients before and after treatment with immunotherapy of chemotherapy. Parasite Immunol 1989; 11:211–222.

92. Monjour L, Mansouri P, Cubas AC, et al. Immunotherapy as treatment of cutaneous leishmaniasis. J Infect Dis 1991; 164:1244–1245.

93. Olson C, Skidmore LV. Therapy of experimentally produced bovine cutaneous papillomatosis with vaccines and excision. J Am Vet Med Assoc 1959; 135:339–343.

94. Pearson JKL, Kerr WR, McCartney WDJ, Steele THJ. Tissue vaccines in the treatment of bovine papillomas. Vet Record 1958; 79:971–973.

95. Anonymous. Treatment of warts in cattle. Mod Vet Pract 1978; September: 651–652.

96. Campo MS, Grindlay GJ, O'Neil BW, et al. Prophylactic and therapeutic vaccination against a mucosal papillomavirus. J Gen Virol 1993; 74:945–954.

97. Kimbauer r, Chandrachud LM, O'Neil BW, et al. Virus-like particles of bovine papillomavirus type 4 in prophylactic and therapeutic immunization. Virology 1996; 219:47–44.

98. Campo MS. Infection by bovine popillomavirus and prospects for vaccination. Trends Microbiol 1995; 3:92–97.

99. Selvakumar R, Borenstein LA, Lon Y-L, et al. Immunization with nonstructural proteins E1 and E2 of cottontail rabbit papillomavirus stimulates regression of virus-induced papillomas. J Virol 1995; 69:602–605.

100. Malison MD, Morris R, Jones LW. Autogenous vaccine therapy for condyloma acuminatrum: A double-blind controlled study. Br J Vener Dis 1982; 58:62–65.

101. Ablin RJ, Curtis WW. Condylomata acuminata: Treatment by autogenous vaccine. Illinois Med J 1975; 147:343–346.

102. Vuori J, Alfthan O, Pyrhonen S, et al. Treatment of condyloma acuminata in male patients. Eur Urol 1977; 3:213–215.

103. Abcarian H, Smith D, Sharon N. The immunotherapy of anal condyloma acuminatum. Dis Colon Rectum 1976; 19:237–244.

104. Wiltz OH, Torregrosa M, Wiltz O. Autogenous vaccine: the best therapy for perianal condyloma acuminata? Dis Colon Rectum 1995; 38:838–841.

105. Cason J, Khan SA, and Best JM. Towards vaccines against human papillomavirus type-16 genital infections. Vaccine 1993; 11:603–611.

106. Meigner B. Vaccination against herpes simplex virus infections. In: Roizman B, Lopez C, eds. The Herpesviruses: Immunobiology and Prophylaxis of Human Herpesvirus Infection. New York: Plenum Press, 1985:265–296.

107. Anderson SG, Hamilton J, Williams S. An attempt to vaccinate against herpes simplex. Aust J Exp Biol Med Sci 1950; 28:579–584.

108. Hall MJ, Katrak K. The quest for a herpes simplex virus vaccine: Background and recent developments. Vaccine 1986; 4:138–150.

109. Kern AB, Schiff BL. Vaccine therapy in recurrent herpes simplex. Arch Dermatol 1964; 89:844–845.

110. Weitgasser H. Controlled clinical study of herpes antigens Lupidon-H and Lupidon-G. Z Hautkr 1977; 52:625–628.

111. Dundarov S, Andonov P. Seventeen years of application of herpes vaccine in Bulgaria. Acta Virol 1994; 38:205–208.

112. Stanberry LR. Herpes simplex virus vaccines as immunotherapeutic agents. Trends Microbiol 1995; 3:244–247.

113. Ho RJ, Burke RL, Merigan TC. Antigen-presenting liposomes are effective in treatment of recurrent herpes simplex virus genitalis in guinea pigs. J Virol 1989; 63:2951–2958.

114. Burke RL, Goldbeck C, Ng P, et al. The influence of adjuvant on the therapeutic efficacy of a recom-

binant genital herpes vaccine. J Infect Dis 1994; 170:1110–1119.

115. Nesbum AB, Burke RL, Ghiasi H, et al. Vaccine therapy for ocular herpes simplex virus (HSV) infection: Periocular vaccination reduces spontaneous ocular HSV type 1 shedding in latently infected rabbits. J Virol 1994; 68:5084–5092.

116. Stanberry LR, Bernstein DI, Burke RL, et al. Vaccination with recombinant herpes simplex virus glycoproteins: Protection against initial and recurrent genital herpes. J Infect Dis 1987; 155: 914–920.

117. Wachsman M, Aurelian L, Smith CC, et al. Protection of guinea pigs from promary and recurrent herpes simplex (HSV) type 2 cutaneous disease with vaccinia virus recombinants expressing HSV glycoprotein D. J Infect Dis 1987; 155:1188–1197.

118. Berman PW, Vogt PE, Gregory T, et al. Efficacy of recombinant glycoprotein D subunit vaccines on the development of primary, recurrent, and latent genital infections with herpes simplex virus type 2 in guinea pigs. J Infect Dis 1988; 157: 897–902.

119. Stanberry LR, Harrison CJ, Bernstein DI, et al. Herpes simplex virus glycoprotein immunotherapy of recurrent genital herpes: Factors influencing efficacy. Antiviral Res 1989; 11:203–214.

120. Stanberry LR. Immune parameters in HSV infection: Evaluation of herpes simplex virus vaccines in animals: The guinea pig vaginal model. Rev Infect Dis 1991; 13(suppl 11):S920–S923.

121. Burke RL. Development of a herpes simplex virus subunit glycoprotein vaccine for prophylactic and therapeutic use. Rev Infect Dis 1991; 13(suppl 11):S906–S911.

122. Sanchez-Pescador L, Burke RL, Ott G, Van Nest G. The effect of adjuvants on the efficacy of a recombinant herpes simplex virus glycoprotein vaccine. J Immunol 1988; 141:1720–1727.

123. Straus SE, Corey L, Burke RL, et al. Placebo-controlled trial of vaccination with recombinant glycoprotein D of herpes. Lancet 1994; 344: 1460–1463.

124. Bruster H, Illes A, Molling R, et al. Autovaccination in ARC and AIDS patients: A clinical report and a statistical analysis of nearly 7 years therapy. Int Conf AIDS 1992, 8(3):60 (abstract no. Pub 7066).

125. Scolaro M, Durham R, and Pieczenik G. Potential molecular competitor for HIV. Lancet 1991; 1: 731–732.

126. Mathisen GE, Allen AD, Glover N, Au J. Self-mononuclear cell vaccine as a therapy for HIV disease. Natl Conf Hum Retroviruses Relat Infect 1993.

127. Zagury D, Leonard R, Fouchard M et al. Immunization against AIDS in humans (letter). Nature 1987; 326:249–250.

128. Zagury D, Bernard J, Cheynier R, et al. A group specific anamnestic immune reaction against HIV-1 induced by a candidate vaccine against AIDS. Nature 1988; 332:728–731.

129. Zagury D, Anti-HIV cellular immunotherapy in AIDS (letter). Lancet 1991; 338:694–695.

130. Zagury D, Bernard J, Halbreich A, et al. One-year follow-up of vaccine therapy in HIV-infected immune-deficient individuals: A new strategy. J AIDS 1992; 5:676–681.

131. Salk J. Prospects for the control of AIDS by immunizing seropositive individuals. Nature 1987; 327:473–476.

132. Gibbs CJ Jr, Peters R, Gravell M, et al. Observations after human immunodeficiency virus immunization and challenge of human immunodeficiency virus seropositive and seronegative chimpanzees. Proc Natl Acad Sci USA 1991; 88: 3345–3352.

133. Moss RB, Ferre F, Trauger R, et al. Inactivated HIV-1 immunogen: Impact on markers of disease progression. J AIDS 1994; 7(suppl. 1):S21–S27.

134. Levine AM, Groshen S, Allen J, et al. Initial studies on active immunization of HIV-infected subjects. J AIDS Hum Retrovir 1996; 11:351–364.

135. Ferre F, Moss RB, Daigle A, et al. Viral load in peripheral blood mononuclear cells as surrogate for clinical progression. J AIDS Hum Retrovir 1995; 10(suppl 2):S51–S56.

136. Redfield RR, Birx DL, Ketter N, et al. Phase I Evaluation of the safety and immunogenicity of vaccination with recombinant gp160 in patients with early human immunodeficiency virus infection. N Engl J Med 1991; 324:1678–1684.

137. Redfield RR, Birx DL, HIV-specific vaccine therapy: Concepts, status, and future directions. AIDS Res Hum Retrovir 1992; 8:1051–1058.

138. Vahey M, Birx DL, Michael NL, et al. Assessment of gag DNA and genomic RNA in peripheral blood mononuclear cells in HIV-infected patients receiving intervention with a recombinant gp160 subunit vaccine in a phase I study. AIDS Res Hum Retrovir 1994; 10:649–654.

139. Walker BD. The rationale for immunotherapy in HIV-1 infection. J AIDS 1994; 7(suppl 1):S6–S13.

140. Merigan TC, Kundu SK. Human immunodeficiency virus envelope glycoproteins. J AIDS 1994; 7(suppl 1):S14–S20.

141. Lundholm P, Wahren M, Sandstrom E, et al. Autoreactivity in HIV-infected individuals does not increase during vaccination with envelope rgp160. Immunol Lett 1994; 41:147–153.

142. Sandstrom E, Bratt G, Eriksson L, et al. Therapeutic immunization with HIV gp160 in HIV-seropositive patients. Int Conf AIDS 1994, 10(1), 214 (abstract no. PBO287).

143. Trauger RJ, Daigle AE, Giermakowska W, et al. Safety and immunogenicity of a gp120-depleted, inactivated HIV-1 immunogen: results of a double-

blind, adjuvant controlled trial. J AIDS Hum Retrovir 1995; 10(suppl 2):S74–S82.

144. Trauger RJ, Ferre F, Daigle AE, et al. Effect of immunization with inactivated gp120-depleted human immunodeficiency virus type 1 (HIV-1) immunogen on HIV-1 immunity, viral DNA, and percentage of CD4 cells. J Infect Dis 1994; 169: 1256–1264.

145. Kundu SK, Katzenstein D, Moses LE, Merigan TC. Enhancement of human immunodeficiency virus (HIV)-specific CD4+ and CD8+ cytotoxic T-lymphocyte activities in HIV-infected asymptomatic patients given recombinant gp160 vaccine. Proc Natl Acad Sci USA 1992; 89:11204–11208.

146. Zunich KM, Lane HC, Davey RT, et al. Phase I/ II studies of the toxicity and immunogenicity of recombinant gp160 and p24 vaccines in HIV-infected individuals. AIDS Res Hum Retrovir 1992; 8:1335.

147. Tsoukas C, Fong W, Gill J, et al. A placebo controlled study of a therapeutic vaccine, rgp160 (VAXSYN) for early HIV infection. Int Conf AIDS 1994, 10(1), 47 (abstract no. 160B).

148. Picard O, Lebas J, Imbert JC, et al. Complication of intramuscular/subcutaneous immune therapy in severely immune-compromised individuals. J AIDS 1991; 4:641–643.

149. Biselli R, Loomis LD, Del Bono V, et al. Immunization of HIV-infected patients with rgp160: Modulation of rgp120 antibody spectrotype. J AIDS 1994; 7:1016–1024.

150. VanCott TC, Bethke FR, Kalyanaraman V, et al. Preferential antibody recognition of structurally distinct HIV-1 gp120 molecules. J AIDS 1994; 7: 1103–1115.

151. Loomis LD, Deal CD, Kersey K, et al. Humoral responses to linear epitopes on the HIV-1 envelope in seropositive volunteers after vaccine therapy with rgp160. J AIDS 1995; 10:13–26.

152. VanCott TC, Bethke FR, Burke DS, et al. Lack of induction of antibodies specific for conserved, discontinuous epitopes of HIV-1 envelope glycoprotein by candidate AIDS vaccines. J Immunol 1995; 155:4100–4110.

153. Mascola JR, Snyder SW, Weislow OS, et al. Immunization with envelope subunit vaccine products elicits neutralizing antibodies against laboratory-adapted but not primary isolates of human immunodeficiency virus type 1. J Infect Dis 1996; 173:340–348.

154. Ziegner UH, Peters G, Jolly DJ, et al. Cytotoxic T-lymphocyte induction in asymptomatic HIV-1 infected patients immunized with retrovector-transduced autologous fibroblasts expressing HIV-1IIIB Env/Rev proteins. AIDS 1995; 9:43–50.

155. Warner JF, Irwin M, Laube L, et al. Genetic immunization of humans for AIDS immunotherapy using direct retroviral vector administration. Int Conf AIDS 1994, Aug 7–12;10(2)116 (abstract no. PAO345).

156. Bonhoeffer S, Nowak MA. Can live attenuated virus work as post-exposure treatment? Immunol Today 1995; 16:131–135.